Amendments to the Drawings

The attached sheets of drawings include changes to FIGs. 1B and 2B. These sheets replace the original sheet including FIGs. 1A and 1B and FIGs. 2A and 2B.

Remarks

A. Status of the Claims

Claims 29, 31-38, 47, and 57-58 were pending at the time of the Action. Claims 29, 35, 37, and 47 have been amended for clarity as discussed in more detail below. No new matter was added by these amendments.

B. The Information Disclosure Statement

The Action notes that foreign patent documents WO 2004/014952 A2 and FR 2 843 396 have been placed in the file, but have not been considered because they are not in English. Applicants direct the Examiner's attention to US Patent No. 7,553,937 (IDS Ref. A9), which is the US patent corresponding to WO 2004/014952 A2 and FR 2 843 396.

C. Objection to the Drawings

The Action objects to the shading used in FIG. 1B. Applicants have removed the shading in FIG. 1B, as well as in FIG. 2B. The amino acids that were previously identified by the shading are now written in bold and italics. Applicants request the withdrawal of this objection in view of the amendment to the drawings.

D. Objections to the Specification

The Specification is objected to for containing a hyperlink and because the title is allegedly not descriptive of the currently claimed invention. Applicants request the withdrawal of this objection in view of the amendments to the specification submitted herewith.

E. Sequence Compliance

The Notice to Comply states that Applicants' sequence listing is deficient because it was not accompanied by a statement that the content of the paper copy and computer readable form are the same. This statement, however, is based on a mistaken belief that Applicants submitted

the sequence listing in paper copy and computer readable form. Applicants filed the sequence listing on September 5, 2008, as a text file through EFS-Web. The text file serves as both the paper copy required by 37 CFR 1.821(c) and the CRF required by 37 CFR 1.821(e). Thus, a statement under 37 CFR 1.821(f) indicating that the paper copy and CRF copy of the sequence listing are identical is unnecessary. *See* "Legal Framework for EFS-Web," September 2008, available at http://www.uspto.gov/ebc/portal/efs/legalframework.pdf.

F. Objections to the Claims

The Action objects to informalities in claims 29 and 47. Specifically, the Action objects to the preamble of claim 29 because the language used in the preamble does not match the concluding step of the claim. The Action also objects to a comma in the second-to-last line of claim 29. Finally, the Action objects to claim 47 for using "a" instead of "the." Applicants have amended the preamble of claim 29 to correspond to the language used in the concluding step. Applicants have deleted the comma in the second-to-last line of claim 29. Applicants also have amended claim 47 to recite "the" instead of "a." In view of the above, Applicants request the withdrawal of these objections.

G. Incorporation By Reference

The Action's assertion that the full sequence of canine proBNP must be reproduced in the specification is without merit. For reasons discussed in more detail below with regard to the indefiniteness rejection, the relationship between the sequences recited in the specification and the sequence recited in P16859 would not be ambiguous to a person of ordinary skill in the art. Accordingly, the recitation of a full length proBNP sequence in the specification is not essential. Moreover, there is no *per se* rule that an invention that involves a biological macromolecule must contain a recitation of the molecule's known structure in order to adequately describe the

invention. *See Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006). In addition, it is well established that a patent need not teach, and preferably omits, what is well known in the art. *See Hybridtech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1987). It is, therefore, unnecessary to reproduce the entire amino acid sequence of canine proBNP in the specification when a publicly accessible source, which is identified in the specification, provides the sequence.

H. The Claims Are Enabled

Claims 29, 31-38, 47, and 57-58 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants traverse this rejection.

The Examiner appears to be reading the claim as requiring the ability to distinguish between a full-length proBNP and a fragment of proBNP, which the Examiner asserts would not be possible with an antibody that binds amino acids 32-48 because this antibody would bind both full-length proBNP and NT-proBNP. The method, however, does not require one to distinguish between a full-length proBNP and a fragment of proBNP (*e.g.*, NT-proBNP). The determination is to the presence and/or concentration of canine proBNP whether in its full-length form, as a fragment, or as a mixture of full-length and fragments. To clarify this point, claim 29 has been amended to recite "proBNP and fragments thereof."

With respect to the Action's item (4) concerning the phrase "at least one antibody that binds to at least one epitope ... of canine proBNP," the Examiner's argument is misplaced. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. MPEP § 2164.01(b). Moreover, failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. § 112. MPEP § 2164.01(b). Applicants' specification satisfies the requirement by, for example,

disclosing working examples with several antibodies that bind at least one epitope of canine proBNP. The Examiner's assertion that the specification must enable bispecific antibodies is improperly requiring enablement of a limitation that is not recited in the claim. Applicants do not concede that the claims would not encompass a bispecific antibody or that the specification does not provide enabling disclosure of bispecific antibodies, they are merely noting that a bispecific antibody is not required by the claims nor would it be necessary to make and use the claimed invention.

In view of the above, Applicants request the withdrawal of this rejection.

I. The Claims Are Definite

1. Claims 29, 31-38, 47, and 57-58

The Action rejects claims 29, 31-38, 47, and 57-58 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner alleges that these claims are indefinite because they omit the relationship between the addition of the antibody and the determination of the presence or concentration of proBNP or fragments thereof. Claim 13 has been amended to clarify that the presence and/or concentration of the canine proBNP and fragments thereof is determined by detecting the binding of the antibody to the epitope. Applicants respectfully request the withdrawal of this rejection.

2. Claims 29, 31, 47, and 58

The Action rejects claims 29, 31, 47, and 58 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner asserts that these claims are indefinite because the specification allegedly does not disclose enough information to identify amino acids 20 to 86 of canine proBNP. Applicants traverse this rejection.

One of ordinary skill in the art would be able to identify amino acids 20 to 86 of canine proBNP in light of the specification. The specification discloses sequences of several epitopes of canine proBNP (*see* FIG. 1B), and the specification discloses that the sequence of canine proBNP is published in Swiss-Prot Accession No. P16859. The Action notes that the numbering of canine proBNP epitopes in the specification differs from the numbering used in Swiss-Prot Accession No. P16859. This is because P16859 includes a 26 amino acid signaling peptide that precedes the proBNP (see the "Molecule processing" section on the 2nd page of the Swiss-Prot printout attached to the Office Action). If the signaling peptide was not included in the numbering of the P16859, it would be the same as the numbering used in the specification. This would be readily apparent to one skilled in the art. Furthermore, for reasons already discussed above in the "Incorporation By Reference" section, the Action's assertion that the full sequence of canine proBNP must be reproduced in the specification is without merit. Thus, reference in the claims to specific amino acid sequences by amino acid numbers is sufficient to identify the intended sequences.

In view of the above, the claims satisfy the requirements of 35 U.S.C. § 112, second paragraph. Applicants, therefore, request the withdrawal of this rejection.

3. Claim 37

The Action rejects claim 37 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner notes that the phrase "the at least one further antibody" in claim 37 lacks antecedent basis. Claim 37 has been amended to depend from claim 34, which provides antecedent basis for this phrase. Applicants respectfully request the withdrawal of this rejection.

J. The Rejections Under 35 U.S.C. § 103(a)

1. MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe

The Action alleges that claims 29, 31-33, 37-38, 47, and 57-58 are unpatentable over MacDonald in view of Asada *et al.* (EP 1 016 867 B1), Harlow & Lane, Janeway *et al.*, and Wolfe. MacDonald is said to disclose a positive correlation between BNP-32 levels and cardiac disease in canines. Asada is said to teach that it is indispensable to assay both BNP-32 and pro-BNP in order to accurately diagnose cardiac disease. The Action acknowledges that Asada's example involved human BNP sequences, but the Action asserts that Asada "clearly contemplates" any mammalian proBNP including canine proBNP. The Action, therefore, concludes that it would have been obvious to modify the method of MacDonald to detect not only canine BNP-32 but also proBNP in order to obtain more accurate results. The remaining publications by Harlow & Lane, Janeway *et al.*, and Wolfe are cited for their teachings with respect to antibodies generally. Applicants traverse this rejection.

To establish a *prima facie* case of obviousness the Action must, among other things, establish that there would have been a reasonable expectation of success to achieve the claimed invention. A reasonable expectation of success has not been established in this case because of several unpredictable factors. It was not previously known which fragments of canine proBNP circulated in blood or whether the amount of any such fragments was sufficient to be detected by immunoassay. Asada reported that ***human*** BNP exists primarily in human blood as proBNP rather than BNP-32. Asada does not, however, disclose which form of ***canine*** BNP is predominant in canine blood. The Action merely speculates that Asada's findings concerning human BNP would apply to canines. The MacDonald reference would call such speculation into question.

MacDonald describes a comparative study of human and dog plasma BNP concentrations in which human BNP concentration was shown to increase with age, whereas dog BNP concentration did not show such a correlation with age (p. 175, col. 1). Thus, not all observations regarding circulating concentrations of human BNP apply to canine BNP. Furthermore, the attached alignment (Exhibit 1) of canine and human proBNP sequences shows that there is considerable variation, particularly in the region of amino acids 20-86 of the canine sequence. These differences are further confirmed by Example 4 in the present specification where it was shown that there was low cross reactivity between human Nt-proBNP and antibodies produced against epitopes of canine Nt-proBNP. These structural differences could result in different half-lives and/or different fragmentation patterns for the human and canine proBNP. The Liu reference, which is discussed in more detail below in the context of the rejection in which it was raised, provides further evidence of the unpredictability of making inter-species predictions about proBNP. It would, therefore, have been unpredictable whether one could have successfully modified the method of MacDonald based on the teachings of Asada to arrive at the currently claimed method.

Finally, the Harlow & Lane, Janeway *et al.*, and Wolfe are cited for their teachings with respect to antibodies generally. They provide no teachings regarding canine proBNP that would overcome the unpredictability discussed above.

The current claims are patentable over MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe for at least the reasons discussed above. Applicants, therefore, request the withdrawal of this rejection.

2. MacDonald, Asada, Harlow & Lane, Janeway, Wolfe, and Harlow & Jane 2

Dependent claims 34-36 are rejected as allegedly unpatentable over the MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe references discussed above, further in view of Harlow & Lane 2. Applicants traverse this rejection.

If an independent claim is nonobvious under 35 U.S.C. § 103(a), then any claim depending therefrom is nonobvious. MPEP § 2143.03. For the reasons discussed in the preceding section, claims 29, 31-33, 37-38, 47, and 57-58 are non-obvious over MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe. Thus, dependent claims 34-36 are also non-obvious.

3. MacDonald, Karl, and Liu

Claims 29, 31-38, 47, and 57-58 are rejected as allegedly unpatentable over MacDonald in view of Karl *et al.* (U.S. 2007/0059767) and Liu *et al.*, "Cloning and characterization of feline brain natriuretic peptide," Gene, 292:183-190 (2002). The Action alleges that it would have been obvious to modify the method of MacDonald to detect NT-proBNP instead of BNP-32 in view of the teachings of Karl. Liu is cited as teaching that canine BNP sequences were known and are similar to those from other species. Liu is also cited to support the Action's assertion that with knowledge of a protein's amino acid sequence, antibodies can be produced against the protein in order to detect the protein by clinical immunoassay. Applicants traverse this rejection.

As mentioned above, to establish a *prima facie* case of obviousness the Action must, among other things, establish that there would have been a reasonable expectation of success to achieve the claimed invention. A reasonable expectation of success has not been established in this case because of several unpredictable factors. It was not previously known which fragments of canine proBNP circulated in blood or whether the amount of any such fragments was

sufficient to be detected by immunoassay. Karl reported that ***human*** BNP is more stable than BNP-32. Karl does not, however, discuss the stability of ***canine*** BNP or BNP-32. The Action merely speculates that Karl's findings concerning human BNP would apply to canines. As discussed above, however, the MacDonald reference would call such speculation into question.

MacDonald describes a comparative study of human and dog plasma BNP concentrations in which human BNP concentration was shown to increase with age, whereas dog BNP concentration did not show such a correlation with age (p. 175, col. 1). Thus, not all observations regarding circulating concentrations of human BNP apply to canine BNP. Furthermore, the attached alignment (Exhibit 1) of canine and human proBNP sequences shows that there is considerable variation, particularly in the region of amino acids 20-86 of the canine sequence. These differences are further confirmed by Example 4 in the present specification where it was shown that there was low cross reactivity between human Nt-proBNP and antibodies produced against epitopes of canine Nt-proBNP. This observation is supported by the Liu reference, which stated that "***antibodies of BNP are species specific.***" (Liu, last sentence on page 183). These structural differences in proBNP could result in different half-lives and/or different fragmentation patterns for the human and canine peptides.

Moreover, while figure 3 in the Liu reference shows similarities between the canine and human preproBNP sequence, most of the similarities are in the N-terminal 26 amino acid signaling sequence or the C-terminal BNP-32 region, not in amino acids 20 to 86 of canine proBNP. Furthermore, based on Liu's analysis of the preproBNP sequence alignment, Liu explicitly states that ***"human was a distinct group as compared to the other species"*** and ***"human prepropiptide [sic] has many unique sequences and appears to have evolved independently from other species."*** (Liu, p. 187, 2nd col. and p. 188, 2nd col.) Additionally, Liu

states that the species variations in length and structure supports the species-specific actions of BNP across species. (Liu, p. 188, 2nd col.). Thus, Liu is evidence of the unpredictability of using observations in humans to predict an outcome in canines.

It would, therefore, have been unpredictable whether one could have successfully modified the method of MacDonald based on the teachings of Karl and Liu to arrive at the currently claimed method. Accordingly, Applicants respectfully request the withdrawal of this rejection.

K. The Provisional Obviousness-Type Double Patenting Rejection

Claims 29, 31-38, 47, and 57-58 are provisionally rejected for obviousness-type double patenting over claims 1-20 of co-pending Application No. 12/394,731. A provisional double-patenting rejection is not a final rejection that blocks the prosecution of all of the conflicting applications. If a provisional double-patenting rejection is the only rejection remaining in the earlier filed application, the Examiner should withdraw the rejection and permit the application to issue as a patent without a terminal disclaimer. MPEP § 804(I)(B).

L. Conclusion

Applicants believe this to be a complete response to all issues raised in the Office Action dated March 18, 2009. The Examiner is invited to contact the undersigned attorney at (512) 536-5654 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Travis M. Wohlers
Reg. No. 57,423
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
Telephone: 512/536-5654
Facsimile: 512/536-4598

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